

Name: David Root

Email: david.root@colorado.edu

Ventral tegmental area glutamate neurons establish a mu-opioid receptor gated circuit to mesolimbic dopamine neurons and regulate opioid-seeking behavior

Dillon J McGovern, Abigail M Polter, Annie Ly, Emily D Prevost, Connor J McNulty,
David H Root

University of Colorado Boulder, George Washington University (AMP)

A two-neuron model of ventral tegmental area (VTA) opioid function classically involves VTA GABA neuron regulation of VTA dopamine neurons via a mu-opioid receptor dependent inhibitory circuit. However, this model predates the discovery of a third major type of neuron in the VTA: glutamatergic neurons. We find that about one-quarter of VTA neurons expressing the mu-opioid receptor are glutamate neurons without molecular markers of GABA co-release. Glutamate-Mu opioid receptor neurons are topographically distributed in the anterior VTA. The majority of remaining VTA mu-opioid receptor neurons are GABAergic neurons that are largely within the posterior VTA and do not express molecular markers of glutamate co-release. Optogenetic stimulation of VTA glutamate neurons results in excitatory currents recorded from VTA dopamine neurons that are reduced by presynaptic activation of the mu-opioid receptor *ex vivo*, establishing a local mu-opioid receptor dependent excitatory circuit from VTA glutamate neurons to VTA dopamine neurons. This VTA glutamate to VTA dopamine pathway regulates dopamine release to the nucleus accumbens through mu-opioid receptor activity *in vivo*. Behaviorally, VTA glutamate calcium-related neuronal activity increased following oxycodone consumption and response-contingent oxycodone-associated cues during self-administration and abstinent reinstatement of drug-seeking behavior. Further, chemogenetic inhibition of VTA glutamate neurons reduced abstinent oxycodone-seeking behavior in male but not female mice. These results establish 1) a three-neuron model of VTA opioid function involving a mu-opioid receptor gated VTA glutamate neuron pathway to VTA dopamine neurons that controls dopamine release within the nucleus accumbens, and 2) that VTA glutamate neurons participate in opioid-seeking behavior.